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Renal nerve ablation reduces blood pressure in resistant hypertension: Long-term clinical outcomes in a single-center experience

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[Corrections added on April 2, 2018, after first online publication: The authors Andrea Denegri, Tino Naduvathumuriyil, and Isabella Sudano are not affiliated to Royal Brompton & Harefield Hospital, Imperial College, London, UK.]

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Approximately 10% of patients with hypertension have resistant hypertension, even if adequate pharmacological therapy is established. In this regard, renal nerve ablation (RNA) could represent a valid alternative treatment option. In a retrospective analysis with a follow-up of 6, 12, and 24 months, the authors investigated the efficacy and safety of catheter-based renal artery ablation in 57 patients undergoing RNA with multiple renal nerve ablation in both renal arteries. In addition to medical antihypertensive therapy (4.2 ± 1.4 drugs per patient), RNA using three different ablation systems was performed in patients with confirmed resistant hypertension (systolic blood pressure >140 mm Hg in spite of three drugs including a diuretic). The primary end point was the change in office ambulatory systolic blood pressure from baseline to 6, 12, and 24 months of follow-up after RNA. The primary safety end point was the change in plasma creatinine levels after 12 and 24 months compared with baseline. The mean office systolic blood pressure at baseline was 167.6 ± 22.4 and after 6, 12, and 24 months averaged 143.5 ± 21.1 ($P < .05$), 141.1 ± 21.1 ($P < .05$), and 139.4 ± 19.6 mm Hg ($P < .05$) respectively, with an average of 15.1 ± 5.3 nerve ablations performed. No significant changes in plasma creatinine levels were observed at 12 months ($P = .421$) and at 24 months ($P = .217$). There were no complications after RNA nor any relevant adverse vascular, renal, or cardiovascular events observed except in one patient in whom a covered stent had to be placed at the femoral puncture site. In this study, in all patients with resistant hypertension, RNA, if performed adequately in the number of ablations and energy delivery, is an efficient and safe treatment option to lower office and 24-hour blood pressure. Whether these blood pressure–lowering effects will lead to a reduction of cardiovascular morbidity and mortality will require further studies.

1 | INTRODUCTION

Arterial hypertension is highly prevalent in the overall population, in particular in adults and the elderly, and represents one of the major cardiovascular risk factors for myocardial infarction and stroke.[1,2] Both of these events exhibit a linear relationship with blood pressure (BP) and stroke in particular is tightly linked to elevated BP and age.[3,4] Moreover, high BP is associated with an increased risk of developing vascular dementia.[5] In over 95% of patients, no apparent cause for elevated BP values can be found, a condition that has been defined as essential hypertension.[6] On the other hand, renovascular hypertension is the most common curable form of secondary

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hypertension, accounting for up to 1% to 3% of cases.[7] While secondary forms of hypertension are amenable to interventional and surgical procedures, essential hypertension is managed by lifestyle modifications and the use of antihypertensive drugs. Resistant hypertension is defined by the failure to lower systolic BP (SBP) and diastolic BP (DBP) <140 and <90 mm Hg despite appropriate lifestyle modifications plus a diuretic and two other antihypertensive drugs belonging to different classes at adequate doses.[8] The kidneys play a key role in long-term pressure regulation through the sympathetic nervous systems and its efferent and afferent nerves. Surgical sympathectomy has been shown to reduce BP and mortality in patients with severe hypertension.[9] Based on this observation, percutaneous renal nerve ablation has been developed for the treatment of patients with resistant hypertension.[10] Although some trials have provided evidence for the effectiveness of renal nerve ablation (RNA) in such patients, the Symplicity HTN-3 trial was neutral. However, a subanalysis of Symplicity HTN-3 that analyzed the BP-lowering effects of RNA according to the number of ablations applied, demonstrated a marked BP-lowering effect with 12 or more ablation.[11] Moreover, the results of the SPYRAL HTN-OFF MED trial confirmed BP-lowering efficacy of RNA.[12] Thus, the aim of the present study was to evaluate the long-term efficacy and safety of percutaneous renal denervation in lowering BP in a cohort of patients with resistant hypertension undergoing multiple RNAs in both renal arteries.

2 | PATIENTS AND METHODS

All consecutive 57 patients with pharmacologically resistant hypertension (BP > 140/90 mm Hg) according to the latest European Society of Cardiology guidelines[8] and therapy with at least three antihypertensive drugs, one of which being a diuretic, all at the maximal tolerated doses, referred to the Department of Cardiology of the University Hospital of Zurich from August 2010 and April 2017 were enrolled in the current study with a rate of eight patients per year (Table 1). A secondary form of hypertension was formally excluded in all patients considered in this cohort, during at least two outpatient clinical evaluations. Patients with moderate to severe renal impairment (estimated glomerular filtration rate < 45 mL/min), anatomical contraindications to percutaneous renal denervation, anatomical variants of the renal arteries, short and small renal arteries with a length <20 mm or a diameter <4 mm were excluded. In all patients, antihypertensive therapy had to remain stable for at least 4 weeks before the procedure. All patients were under diuretic therapy and 20 of 57 already assumed an aldosterone antagonist. SBP on admission was >140 mm Hg in all patients. Routine blood analyses and BP measurement were performed before the intervention and at 6, 12, and 24 months in all patients, the latter with an automatic oscillometric device (Microlife or Omron) according to current guidelines. Three different types of renal denervation systems have been used for the procedures by a single experienced operator (T.F.L., Table 2): (1) the Symplicity Renal Denervation System from Medtronic (single electrode, monopolar); (2) the EnligHTN Multi-Electrode Renal Denervation System (multi-electrode basket, monopolar) from St. Jude Medical; and (3) the Vessix Renal Denervation System from Boston Scientific (over-the-wire–based catheter, bipolar). Radiofrequency was erogated through a generator. With the first-generation Symplicity system, the ablation catheter was advanced over a guidewire through a 6F catheter deep close to the bifurcation of the main renal artery, with final application of six ablations in a spiral fashion starting from the distal part of the renal artery up to its origin from the aorta.[13] Commonly, 5 to 8 W are applied for 2 minutes at each of the at least six ablations sites. Impedance may be used to ensure good wall contact (optimal range: 300–350 Ω).

The St. Jude basket contains four electrodes and, once placed distally in the renal artery before the bifurcation, four ablations are automatically applied for 60 seconds. In contrast to the Symplicity system, the St. Jude system is temperature driven. After the first ablation series, multiple ablations are possible by turning the node at the steering end of the ablation catheter and slightly pulling towards the ostium of the renal artery.[14] The Vessix balloon catheter

TABLE 1 Patient characteristics

Characteristics (Patients, N = 57)	No. (%) or mean ± standard deviation
Age, y	61.26 ± 12.25
Male	35/57 (61.4)
BMI	30.93 ± 5.19
Smokers	20 (35.1)
Diabetes mellitus	18 (31.6)
Dyslipidemia	24 (42.1)
CAD	10 (17.5)
CKD	10 (17.5)
COPD	3 (5.3)
AF	4 (7)
Previous stroke	7 (12.3)
Aspirin	27 (47.4)
OAC	5 (8.8)
Diuretics	52 (91.2) 5 (8.8)
Renin inhibitors	7 (12.3)
RAAS inhibitors	49 (86)
Calcium channel blockers	44 (77.2)
β-Blockers	45 (78.9)
α-Blockers	20 (35.1) 2 (3.5)
Nitrates	5 (8.8)
Aldosterone antagonists	20 (35.1)
Average medications	4.24 ± 1.39

AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease, COPD, chronic obstructive pulmonary disease; OAC, oral anticoagulation; RAAS, renin-angiotensin-aldosterone system.

TABLE 2 Devices, producer, technology, and methods of energy delivery of each of the three systems used in our study

	Device	Producer	Technology	Methods	No.	SBP/DBP	SBP/DBP at 6 mo	SBP/DBP at 12 mo	SBP/DBP at 24 mo
	Symplicity	Medtronic	Single electrode monopolar	2 min per ablation	24	173.4 ± 20.9 mm Hg 89.2 ± 15.8 mm Hg	148.1 ± 19.4 mm Hg 84.7 ± 14.0 mm Hg	151.2 ± 21.7 mm Hg 85.5 ± 14.7 mm Hg	151.6 ± 23 mm Hg 87.6 ± 13.9 mm Hg
	EnligHTN	St. Jude Medical	Multi-electrode basket, monopolar	90 s up to four ablation points	14	174.5 ± 17.5 mm Hg 94.3 ± 16.4 mm Hg	145.5.±19.7 mm Hg 85.4 ± 6.2 mm Hg	138.6 ± 19.7 mm Hg 83.1 ± 12.2 mm Hg	133.0 ± 5.7 mm Hg 80.8 ± 9.9 mm Hg
	Vessix	Boston Scientific	Over-the-wire–based catheter, bipolar	30 s up to six ablation points	19	155.3 ± 22.4 mm Hg 87.3 ± 21.3 mm Hg	136.6 ± 21.3 mm Hg 78.9 ± 12.4 mm Hg	126.4 ± 16.5 mm Hg 80.4 ± 12.0 mm Hg	126.2 ± 12.8 mm Hg 74.5 ± 3.2 mm Hg

The Tables also report the mean values of systolic blood pressure (SBP) and diastolic blood pressure (DBP) achieved after renal nerve ablation at 6, 12, and 24 months for each of these three devices.

(Boston Scientific) is an over-the-wire system using bipolar energy, consisting in a low-pressure balloon (3 atm) available in 4-, 5-, 6-, and 7-mm diameter sizes with offset electrode pairs placed in a helical pattern. With simple anatomy, the balloon can be easily advanced into the renal artery over a 0.014 F guidewire.[15] BP was measured with an automatic oscillometric device (Microlife or Omron) while the patient was sitting for 5 minutes and using a 24-hour BP recorder (SpaceLabs) before and at 6, 12, and 24 months after the RNA procedure. RNA was performed using a full four-quadrant ablation technique on both renal arteries, from the distal to the proximal segment, with energy delivery performed for all the time required from each system. The primary end point was the change in systolic and diastolic office BP values at 6, 12, and 24 months compared with baseline immediately before the index procedure. The primary safety end point was the change in plasma creatinine levels at 12 and 24 months compared with baseline immediately before the index procedure. The 6-month follow-up was optional for the patients; 24 patients completed follow-up with 24-hour ambulatory BP monitoring (ABPM) and only 28 with an office measurement. At 24 months, only 11 patients were investigated with 24-hour ABPM, while 21 accepted a clinical follow-up. All results are reported as means ± standard deviations. A *t* test was performed for all statistical analyses and statistical significance was set at $\alpha \le 0.05$. All statistical analyses were performed with SPSS version 22.0 (IBM).

3 | RESULTS

After RNA, a significant reduction of systolic and diastolic BP was observed at 6, 12, and 24 months (Figure 1). The mean office SBP value was 167.6 ± 22.4 mm Hg at baseline and 143.5 ± 21.1, 141.1 ± 21.1, and 139.4 ± 19.6 mm Hg after 6, 12, and 24 months, respectively (all $P < .05$, compared with baseline). The mean 24-hour systolic ABPM values at baseline averaged 154.8 ± 18.4 mm Hg and 142.4 ± 21.8, 137.7 ± 17.4, and 139.9 ± 11.8 mm Hg at 6, 12, and 24 months, respectively (all $P < .05$, compared with baseline). Similar results were also observed when considering the mean diastolic values for the office and 24-hour measurements. Compared with the baseline value of 89.8 ± 18.36 mm Hg, DBP fell to 83.3 ± 12.2 ($P < .05$), 83.0 ± 12.2 ($P < .05$), and 82.5 ± 12.3 mm Hg ($P \le .05$) for office measurements and from 89.8 ± 18.3 mm Hg to 83.3 ± 12.2 ($P = .02$), 83.0 ± 12.2 ($P \le .05$), and 82.5 ± 12.3 ($P \le .05$) for 24-hour ABPM (Table 3 and Table 4). The small difference between ABPM and office values is the result of the limited number of ABPM measurements available (9 of 57 patients at 24 months). A nonparametric test with related samples was applied to both ABPM and office measurements. Regarding ABPM, we found a significant reduction from the baseline for SBP at 6 months ($P < .05$) and at 12 months ($P = .05$), but not at 24 months ($P = .19$), as well as for DBP at 6 ($P < .05$), 12 ($P = .02$), and 24 ($P = .32$) months. Analyzing the office BP measurements, we found a statistically significant reduction for SBP at 6 ($P = .02$) but not at 12 ($P = .45$) and 24 ($P = .45$) months, as well as for DBP at 6, 12, and 24 months (all $P > .05$). The

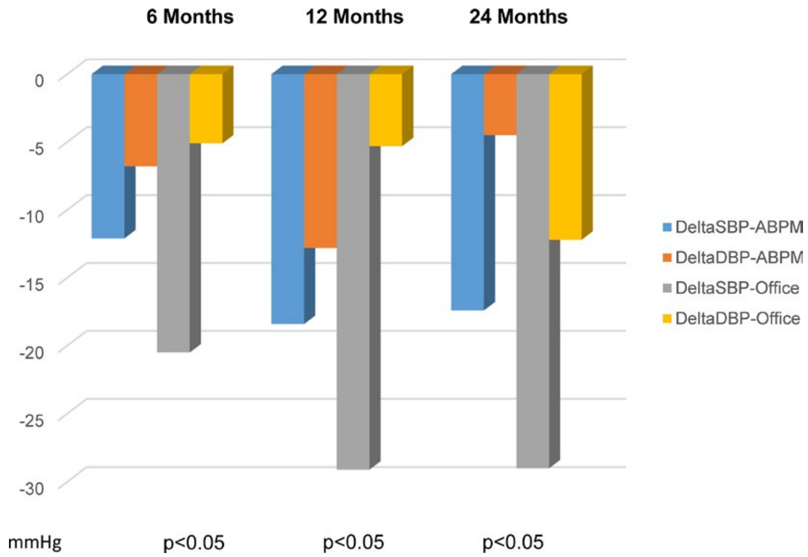

FIGURE 1 Mean systolic and diastolic blood pressure reduction according to 24-hour ambulatory blood pressure monitoring (ABPM) and office measurements. DeltaSBP-ABPM = systolic blood pressure difference according to 24-hour ambulatory blood pressure measurement (−12.1, −18.4, and −17.4 mm Hg); DeltaDBP-ABPM = diastolic blood pressure difference according to 24-hour ambulatory blood pressure measurement (−6.8, −12.8, and −4.5 mm Hg); DeltaSBP-Office = systolic blood pressure difference according to office blood pressure measurement (−20.5, −29.1, and −29 mm Hg); DeltaDBP-Office = diastolic blood pressure difference according to office ambulatory blood pressure measurement (−5.1, −5.3, and −12.2 mm Hg). Compared with baseline, all of these differences were statistically significant ($P < .05$)

TABLE 3 24-Hour ABPM at baseline and at 6,12, and 24 months after renal nerve ablation

ABPM (Patients, N = 57)	
SBP at baseline (n = 46)	154.8 ± 18.4
DBP at baseline	88.7 ± 13.6
SBP at 6 mo (n = 32)	142.4 ± 21.8 ($P < .05$)
DBP at 6 mo	81.0 ± 12.4 ($P < .05$)
SBP at 12 mo (n = 19)	137.7 ± 17.4 ($P = .05$)
DBP at 12 mo	78.6 ± 9.8 ($P = .02$)
SBP at 24 mo (n = 9)	139.9 ± 11.8 ($P = .19$)
DBP at 24 mo	82.0 ± 8 ($P = .32$)

ABPM, ambulatory blood pressure monitoring; DBP, diastolic blood pressure; SBP, systolic blood pressure.

TABLE 4 Office BP measurement at baseline and at 6, 12, and 24 months after renal nerve ablation

Office BP measurement (Patients, N = 57)	
SBP at baseline (n = 57)	167.6 ± 22.4
DBP at baseline	89.8 ± 18.3
SBP at 6 mo (n = 44)	143.5 ± 21.1 ($P = .02$)
DBP at 6 mo	83.3 ± 12.2 ($P = .05$)
SBP at 12 mo (n = 29)	141.1 ± 21.1 ($P = .45$)
DBP at 12 mo	83.0 ± 12.2 ($P > .05$)
SBP at 24 mo (n = 23)	139.4 ± 19.6 ($P = .45$)
DBP at 24 mo	82.5 ± 12.3 ($P > .05$)

BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.

average number of ablations was 15.1 ± 5.3 (11.9 ± 2.8 until 2013 and 19.4 ± 4.6 from 2014) performed with the Symplicity RDN System from Medtronic (n = 24 patients, 2 minutes per ablation), with the EnligHTN Multi-Electrode Renal Denervation System from St. Jude Medical (n = 14 patients, 90 seconds up to four ablation points) and with the Vessix Renal Denervation System from Boston Scientific (n = 19 patients, 30 seconds up to six ablation points). There was no statistically significant difference in lowering efficacy between the three different systems used (all $P > .05$). There were no short- or long-term complications after the intervention and no relevant adverse vascular, renal, or cardiovascular events observed except in one patient in whom the procedure had to be postponed after introducing the sheet because of marked bleeding from the puncture site, which was treated with implantation of a covered stent. The RNA procedure was then performed a few weeks later. All 57 patients were discharged at home the day after the procedure. There was no significant correlation between baseline characteristics and BP reduction, except for the assumption of an aldosterone antagonist before RNA and the reduction of both office SBP and DBP at 6 months ($P = .046$ and $P = .003$, respectively) but not at 12 and 24 months. The lack of significance at follow-up is likely attributable to the limited number of patients.

Follow-up was the major limitation of the study. ABPM was available for 39, 26, and 12 patients at 6, 12, and 24 months, respectively, while office measurement was available for 44, 31, and 23 patients. Considering the office measurement, according to the international guidelines, we found that at 6, 12, and 24 months, only 16 (SBP 119.9 ± 12.7 mm Hg, DBP 76.9 ± 10.5 mm Hg), 11 (SBP 118.2 ± 10.4 mm Hg, DBP 73.6 ± 9.3 mm Hg), and 13 (SBP 126.3 ± 8.8 mm Hg, DBP 77 ± 6.6 mm Hg) of 57 patients presented

TABLE 5 Creatinine levels at baseline and at 12 and 24 months after renal nerve ablation

Laboratory test (patients, N = 57)	
Creatinine at baseline (n = 49)	90.8 ± 30.1
Creatinine at 12 mo (n = 36)	91.6 ± 25.1 (*P* = .421)
Creatinine at 24 mo (n = 25)	90.0 ± 27.6 (*P* = .217)

with controlled BP after RNA. Plasma creatinine levels remained stable throughout the observation period, with no significant changes at 12 (*P* = .421) and 24 (*P* = .217) months. No significant changes were observed regarding the number of medications at 6, 12, and 24 months (all *P* > 0.05, Table 5). Of note, only 3 of 37 patients without previous antialdosterone therapy were treated with this drug.

4 | DISCUSSION

In this registry of consecutive patients treated in a single center by one operator who performed an average of 15 ablations in both renal arteries, RNA led to a marked reduction of SBP and DBP without changes in antihypertensive medication or significant side effects. RNA using three different ablation systems was performed in patients with confirmed resistant hypertension: (1) Symplicity Renal Denervation System from Medtronic (n = 24); (2) the EnligHTN Multi-Electrode Renal Denervation System from St. Jude Medical (n = 14); and (3) the Vessix Renal Denervation System from Boston Scientific (n = 19). Our results confirm the results of some international studies on renal denervation.[16–19] Indeed, the Prague-15 study[18] and the DENERHTN (Renal Denervation for Hypertension) study,[19] which had a comparable number of patients, achieved similar BP reductions of 12.4 ± 4.6 and 15.1 ± 5.5 mm Hg, respectively, with a less pronounced reduction at 6 months compared with our results. Furthermore, our study led to similar SBP and DBP reductions 24 months after RNA (28.4 ± 23.95 vs. 28.9 ± 4.6 mm Hg) as the Symplicity HTN-1 registry.[16] In addition, comparable results were obtained in the randomized Symplicity HTN-2 trial.[17]

In contrast, the Symplicity HTN-3 study failed to achieve the primary end point and revealed an overall nonsignificant reduction in BP after RNA compared with the drug only therapy group. The negative results of the large Symplicity HTN-3 study led to a wide interpretation of the study results.[20] Several aspects of the study have been criticized. First, the Symplicity HTN-3 trial included patients in whom BP and antihypertensive drugs had not been stabilized before the intervention. Second, the percentage of black patients was 25% higher than in other studies. This is particularly in contrast to European and Australian studies as well as the current Swiss registry.[21] Indeed, black patients often have low renin and volume-dependent hypertension, which may not respond to RNA. Third, the majority of Symplicity HTN-3 trial patients had already been treated with an average of 5.2 ± 1.4 antihypertensive drugs,[22] which makes it difficult to provide further BP lowering with any intervention. Finally, one of the major issues, on which the researchers of the field focused their attention in the past years, concerns the technical performance of RNA in the Symplicity HTN-3 study. Of note, most of the cardiologists involved in the study had no previous experience with the procedure and, in most of the cases, they accounted for only one or two interventions of this type in the trial. Furthermore, the number of ablations that correlates directly with the degree of BP reduction[11] has been variable in the Symplicity HTN-3 trial, ranging from one to 18 ablations. Importantly, only 84% of the procedures produced complete ablations of 120 seconds, and a bilateral four-quadrant ablation was achieved in only 6% of all patients. In a small subpopulation of 19 patients, who received bilateral four-quadrant ablation, the BP reduction also averaged 24.3 ± 10.3 mm Hg, similar to other studies and the current Swiss registry. Indeed, in the present series of patients, the experienced single operator performed an average of 15 ablations, a number that also showed in the subanalysis of Symplicity HTN-3 a marked and sustained BP-lowering effect of similar size. Thus, it appears that it is essential to perform a large number of ablations in order to destroy the renal nerves within the adventitia and to achieve a relevant BP-lowering effect. Post hoc analysis identified predictors of SBP change in the patients in the Symplicity HTN-3 trial, particularly severe baseline systolic hypertension (SBP > 180 mm Hg), aldosterone antagonist use, nonuse of vasodilators, and, in the denervation group, the number of ablations, which, if delivered in a four-quadrant pattern, led to greater reduction of office and ambulatory SBP and heart rate in this population.[11]

Based on the current controversy on the effectiveness of RNA, a European group of experts discussed the study design for future clinical trials during a consensus conference on RNA.[23] According to this expert opinion paper, RNA should be performed in relatively young patients with mild hypertension, as young patients present with higher sympathetic activity. In the current registry, patients were relatively young, with a median age of approximately 60 years. Indeed, in elderly patients with hypertension, who usually present with isolated systolic hypertension, RNA has been shown to be much less effective.[24] Hence, in this registry, patients with isolated systolic hypertension were not included. Another open question is related to the type of system that should be used for RNA, the type of ablation, and its duration. Balloon-based catheters, as used partially in this study, are probably better and provide a more consistent bilateral four-quadrant ablation in the distal part of the artery. Also, 24-hour ABPM should be the only measurement tool to assess changes in BP, as also performed in this study. Indeed, 24-hour ABPM is important to validate resistant hypertension.[25] The results of the SPYRAL HTN-OFF MED (Global Clinical Study of Renal Denervation With the Symplicity Spyral Multi-electrode Renal Denervation System in Patients With Uncontrolled Hypertension in the Absence of Antihypertensive Medications) trial[12] confirmed the BP-lowering efficacy of RNA and encouraged the design of a larger pivotal trial. In the 80 patients analyzed, there was a significant reduction in office and 24-hour ABPM at 3 months in patients with mild to moderate hypertension after RNA without antihypertensive therapy, which was not observed in the sham control group (24-hour SBP −5.0 mm Hg (95% confidence interval, −9.9 to −0.2; *P* = .0414), 24-hour DBP −4.4 mm Hg (95% confidence interval, −7.2 to −1.6; *P* = .0024), office SBP −7.7 mm Hg (95% confidence interval, −14.0 to −1.5; *P* = .0155), and office DBP −4.9 mm Hg (95% confidence interval, −8.5 to −1.4; *P* = .0077). The retrospective and observational approach, together with the absence of a control arm and pharmacological or sham-procedure, represents the main limitation of the study, considering the profound placebo effect of RNA shown in controlled trials.

5 | LIMITATIONS OF THE STUDY

Our study confirms findings from previous studies demonstrating the safety and efficacy of RNA in a cohort of patients with resistant hypertension. The retrospective analysis, the lack of a control group, and the limited number of patients available at follow-up represent the major limitations of this study. Repeated ABPM was the major complaint of the patients.

6 | CONCLUSIONS

Our real-world experience confirms that RNA leads to an efficient and safe BP reduction in patients with resistant hypertension, if adequately presented in the number of ablations and energy delivery by an experienced operator. Importantly, office and 24-hour BP values after 24 months remained stable compared with those after 12 months, excluding a significant degree of reinnervation in these patients.

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